REMARKS

Claims 1-24 are pending. Reconsideration in view of the following remarks is respectfully requested.

Applicants' undersigned representative wishes to thank Examiner Gollamudi for her time and helpful suggestions in the telephone interview held on August 21, 2002, during which the pending claims and prior art were discussed.

Examiner's Response to Applicants' Arguments

Applicants note that in response to Applicants' prior arguments the Examiner has acknowledged that the claimed invention is not anticipated by U.S. 5,571,841 to Yu et al. However, the Examiner has taken the position that "Yu et al. suggest the instant invention and the mere optimization of the amount of actives is within the skill of the practioner in the art." (Office Action, page 2.)

As will be addressed in greater detail below, the present invention is decidedly not a case of "mere optimization" of actives. The present invention provides compositions that allow for the delivery of greater concentrations (e.g. 5% or more) of a piperidinopyrimidine derivative, such as minoxidil, without the necessity of utilizing large amounts of propylene glycol, or other polyols. This is achieved in the present invention by adjusting the acid concentration of the composition. Prior to Applicants' discovery, it was not predictable that greater concentrations of minoxidil could be achieved in formulation without also using large amounts of propylene glycol or other polyols. Rather, prior to Applicants' discovery, conventional formulations of minoxidil typically contained large amounts of propylene glycol or other polyols in order to solubilize the minoxidil.

Rejection under 35 U.S.C. § 103 over Yu and Kasting

Claims 1-24 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Yu et al. (US 5,571,841) by itself or in combination with Kasting, et al. (US 5,041,439) or vice-versa. Applicants respectfully traverse the rejection.

As already mentioned, compositions according to the present invention allow for the delivery of greater concentrations of a piperidinopyrimidine derivative, such as minoxidil, without the necessity of utilizing large amounts of propylene glycol, or other polyols. This is achieved in the present invention by adjusting the acid concentration of the composition. Using this approach, the amount of active ingredient piperidinopyrimidine derivative in the composition can be significantly increased, e.g., up to levels from approximately 5%-25% by weight of the composition. (See, e.g., page 2, lines 15-23.)

Yu et al.

Yu et al. is directed to the use of hydroxyacids to enhance the "therapeutic efficacy of cosmetic and pharmaceutical agents." (column 2, lines 16-21.) In particular, Yu et al. is teaches the use of "hydroxycarboxylic acids and related compounds" as "enhancing compounds" to enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders, or other afflictions. (column 2, lines 16-42.) Yu, et al, however, is not concerned with and does not even remotely address the problem which the present invention solves, namely, increasing minoxidil amounts while minimizing amounts of propylene glycol, or other polyols. And Yu et al. clearly does not disclose or suggest the composition of claim 1, which specifically requires "at least 5% by weight" of a "piperdinopyrimidine derivative or a pharmaceutically acceptable salt thereof," "an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or pharmaceutically acceptable salt thereof," and propylene glycol, if present at all, in an amount of "less than approximately 10% by weight."

The Examiner's particular references to Example 3, column 6, lines 51-53, and column 7, lines 1-3 of Yu et al. do not provide the requisite suggestion to specifically modify the disclosed formulations of Yu et al. to arrive at the claimed formulation, nor is there any indication or hint in Yu et al. that the composition of claim 1 having a high minoxidil concentration and low propylene glycol concentration could even be obtained.

Example 3 of Yu et al. describes a "2% minoxidil" formulation formed by dissolving 2 grams minoxidil and 3 ml lactic acid into a mixture of 80 ml ethanol and 15 ml propylene glycol. A 2% minoxidil formulation is much less than the claimed composition which requires 5% or greater of a piperidinopyrimidine derivative, such as minoxidil. In addition, the formulation of Example 3 has a large propylene glycol content, 15%, which is substantially greater than the "less than approximately 10% by weight" of propylene glycol required by claim 1. The formulation of Example 3 does include lactic acid, but there is no suggestion, implied or otherwise, in Yu et al., that the addition of specific amounts of acid could result in a formulation having both 5% or greater minoxidil and less than 10% propylene glycol. Thus, the formulation exemplified in Example 3 of Yu et al. cannot be taken as providing a teaching or suggestion of the particular composition of claim 1.

The disclosure at column 6, lines 51-53 of Yu et al. likewise does not teach or suggest the particular composition of claim 1. Here, Yu et al. states broadly that "[t]he concentration of the cosmetic or pharmaceutical agent" of the Yu et al. compositions "ranges from 0.01 to 40 percent by weight of the total composition." Such a broad statement speaks nowhere to a specific formulation having both 5% or greater minoxidil and less than 10% propylene glycol.

Finally, column 7, lines 1-3 of Yu, list a "typical gel composition" according to the Yu et al. invention that includes an hydryoxyacid and a cosmetic or pharmaceutical agent "dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively." Again, this provides no teaching or suggestion as to a specific formulation having both 5% or greater minoxidil and less than 10% propylene glycol. In fact, it suggests the opposite, namely, a formulation having a high propylene glycol concentration, namely, 20%.

Kasting et al.

Unlike Yu, et al., Kasting, et al. is particularly directed to topical compositions containing hydroxy imminopyrimidine pharmaceuticals, including minoxidil. However, Kasting, et al. provides no teaching or suggestion as to a specific formulation having both 5% or greater minoxidil and less than 10% propylene glycol. Rather, Kasting, et al. focuses on the use of polar lipid compounds together with diol or triol compounds to improve topical delivery of hydroxy iminopyrimidine compounds, such as minoxidil. (column 2, lines 29-36.) In particular, the formulations of Kasting, et al. include a hydroxy iminopyrimidine compound, such as minoxidil, together with a "penetrating enhancing vehicle" containing "a C_3-C_4 diol, such as propylene glycol, or a C_3-C_6 triol, such as 1,2,6-hexanetriol, together with a polar lipid compound selected from C_{16} mono-unsaturated alcohols, C_{16} branched chain saturated alcohols and C_{18} mono-unsaturated and branched chain saturated alcohols, such as oleyl alcohol or isocetyl alcohol." (column 4, lines 26-35, emphasis added) In other words, Kasting, et al. attempts to enhance penetration of minoxidil by *adding* a lipid component to a formulation containing a diol, such as propylene glycol, or a triol. But Kasting, et al. is not pursuing ways to increase amounts of minoxidil while *minimizing* the diol or triol concentrations, nor does Kasting, et al. suggest in any way that such can be accomplished through the use of acid. (Note that the use of acid salts of minoxidil, as noted in column 6, lines 44-53 of Kasting, et al., is not a teaching or suggestion of using acid to achieve a formulation having a high concentration of minoxidil and low concentration of a diol or triol.)

Suggestion or motivation to specifically combine/modify aspects of cited references to arrive at claimed invention has not established

Under 35 U.S.C. §103(a), a claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter *as a whole* would have been obvious *at the time the invention was made* to a person having ordinary skill in the art." (emphasis added.) In determining obviouis, it is critical not to engage in hindsight analysis; rather, measuring a

claimed invention against the obvious standard established by 35 U.S.C. §103 "requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Close adherence to the above is especially important in cases where the ease with which the invention is understood may prompt one to "fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." Id., 50 USPQ2d at 1617 (citing *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983).

Rigorous application of the requirement for showing of the teaching or motivation to combine and/or modify references is the best defense against hindsight-based obviousness analysis. Id., 50 USPQ2d at 1617. Further, there is a pervasive need for specificity in such showings. *In re Lee*, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002). Indeed, where a claim recites a combination of elements, *particular* findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected certain components for combination *in the manner claimed*. *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). Similarly, "there is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention." *Smith Indus. Med. Sys., Inc. v. Vital Signs, Inc.* 51 USPQ2d 1415, 1420 (Fed. Cir. 1999). Also, the mere fact that references can be combined or modified does not render the resultant combination obvious absent a suggestion in the prior art of the desirability of the particular combination or modification. *In re Mills*, 916 F.2d 680, 16 USPQ 2d 1430 (Fed. Cir. 1990).

With the above in mind and turning to the instant Office Action, it can be seen that the Office has failed to provide an adequate showing of the specific suggestion or motivation in the art to combine and/or modify the Yu, et al. to arrive at composition having all the recited

elements combined in the manner as claimed in claim 1. Rather the Office merely states the following:

> Although, Yu does not provide a specific example, it is deemed obvious to one of ordinary skill in the art, in the absence of showing unexpected results, to manipulate the conditions to obtain the best possible results since Yu et al provides the general guidance of the hair treating composition. One would be motivated to change the concentration of minoxidil depending on the severity of the condition. Further, Kasting et al teaches a hair loss composition and manipulating the solvent system and active agent to obtain a therapeutic composition without irritation.

(Office Action, pages 3-4.) Thus, the only "motivation" set forth to combine and/or modify Yu et al. or Kastings et al. is one to "manipulate the conditions to obtain the best possible results" and to "change minoxidil concentrations depending on severity." But this is merely asserting that one skilled in the art would be motivated to improve upon known minoxidil formulations. At best, this establishes that it might be "obvious to try" changing the parameters of known minoxidil formulations to achieve an improved formulation, but *in no way* does this general motivation satisfy the requirements developed under 35 U.S.C. §103. As noted above, obviousness under 35 U.S.C §103 requires specific findings as to a suggestion or motivation to combine and/or modify the prior art to achieve the claimed invention as a whole. In this case, that means specific findings as to a suggestion or motivation to combine and/or modify the prior art to achieve the composition having the claimed combination of elements in the manner that is claimed. *See In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

As previously noted, there is no suggestion, implied or otherwise, in Yu et al. or Kastings, et al. that the addition of specific amounts of acid could result in a formulation having both 5% or greater minoxidil and less than 10% propylene glycol. Kastings, et al. in fact essentially teaches away from the present invention, as the high minoxidil concentrations of Kastings, et al. also include high concentrations of propylene glycol, or other diols or triols. Numerous other prior art formulations also teach away from the present invention by requiring high percentages of propylene glycol or similar diol or triol to achieve high minoxidil

concentrations, i.e. greater than 5%. (See specification, page 1, lines 11-21.) Thus, no suggest or motivation has been provided to modify Yu et al. or Kastings et al. to arrive at a composition specifically as recited in claim 1. Absent a specific suggestion or motivation to manipulate Kastings, et al. and/or Yu et al. to arrive at the particular claimed combination of claim 1, a *prima facie* case of obviousness simply has not been made.

Based on the above, Applicants respectfully submit claim 1 is patentable over Yu et al. and/or Kastings, et al., as are claims 1-20 depending therefrom, and request withdrawal of the rejection as to these claims.

Claim 21 is directed to a method for the treatment of hair loss and related indications, the claimed method including the step of providing a pharmaceutical composition which is primarily as recited in claim 1. As discussed, Yu et al. and/or Kastings, et al. either alone or in combination do not teach or suggest the composition of claim 1 and therefore cannot be considered to teach or suggest a method of using such a composition. Applicants submit method claim 21, as well as claims 22-24 depending therefrom, are thus likewise patentable over Yu et al. and/or Kastings, et al. and request withdrawal of the rejection as to these claims.

Rejection under 35 U.S.C. § 103 over Yu, Kasting and Uchikawa

Claims 11 and 24 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Yu et al. (US 5,571,841) by itself or in combination with Kasting, et al. (US 5,041,439) or vice versa, in further view of Uchikawa, et al. (US 5,156,836). Applicants respectfully traverse the rejection.

Yu et al. and Kasting et al. have been discussed above.

Uchikawa et al. is directed to hair revitalizing tonics containing amine oxide. The reference is specifically relied upon as teaching the use of benzyl alcohol as a solvent and certain ratios of water/ethanol mixtures.

The deficiencies of Yu et al. and Kastings, et al. with respect to the claimed invention have been discussed above. Putting aside the issue of whether one skilled in the art would indeed be motivated to combine Yu et al. and/or Kastings, et al. with Uchikawa et al., the addition of the benzyl alcohol or the water/ethanol mixtures of Uchikawa to the formulations of Yu et al. and/or Kastings, et al., still would not achieve or suggest a specific formulation having both 5% or greater minoxidil and less than 10% propylene glycol. Neither would such a combination teach or suggest a method of using such a composition.

Applicants therefore submit claims 11 and 24 are patentable over Yu et al. and/or Kastings, et al. in view of Uchikawa et al. and request withdrawal of the rejection.

CONCLUSION

Applicant has, by way of the remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would further expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 468452000400.

Respectfully submitted,

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